AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

One Wales Medicines Assessment Group (OWMAG)

Minutes of the hybrid meeting held Monday 19 December 2022

Members in attendance:
In person:
John Watkins, Consultant in Public Health, OWMAG Chair
Andrew Champion, Assistant Director, Evidence Evaluation, representative WHSSC
Alan Clatworthy, Clinical Effectiveness and Formulary Pharmacist, representative Swansea Bay
On Teams:
Joe Ferris, Operations Manager, ABPI Cymru Wales
Teena Grenier, Medicines Governance Lead, representative Betsi Cadwaladr
Kathryn Howard, Head of Pharmacy, Royal Glamorgan Hospital, representative Cwm Taf Morgannwg
William King, Consultant in Public Health, representative Powys
Hywel Pullen, Assistant Director of Finance, Cardiff and Vale, representative Finance Directors
Berni Sewell, Senior Lecturer, Health Economist, Swansea University
Jonathan Simms, Clinical Director of Pharmacy, representative Aneurin Bevan
Michael Thomas, Consultant in Public Health, representative Hywel Dda

AWTTC:
Gail Woodland, Senior Appraisal Pharmacist
Clare Elliott, Senior Appraisal Scientist
Rosie Spears, Senior Appraisal Scientist
David Haines, Medical Writer
Carolyn Hughes, Medical Writer
Rachel Jonas, Medical Writer
Bridget-Ann Kenny, Medical Writer
Laura Phillips, Admin Supervisor

Clinical experts:
Dr Nicola-Xan Hutchinson, Consultant in Respiratory Medicine, Cardiff and Vale UHB
Dr Amar Wahid, Consultant Paediatric Gastroenterologist, Cardiff and Vale UHB
Jessica Girvan, Clinical Pharmacist for Paediatric Gastroenterology and Parenteral Nutrition, Cardiff and Vale UHB

Patient organisation representatives:
Amy Deptford, Policy Manager, Crohn's and Colitis UK
Chloe Hutchinson, Policy Lead (Wales), Crohn's and Colitis UK

Observer(s):
Julie Wilson-Thomas, prospective lay member
Richard O'Connell, Lead Pharmacist – National Cancer Medicines Advisory Group (NCMAG) Programme

List of Abbreviations:

ABPI	Association of the British Pharmaceutical Industry
AWTTC	All Wales Therapeutics and Toxicology Centre
ESR	Evidence Status Report
IPFR	Individual Patient Funding Request
NICE	National Institute for Health and Care Excellence
NMG	New Medicines Group
OWMAG	One Wales Medicines Assessment Group
WHSSC	Welsh Health Specialised Services Committee

1. Welcome and Introduction

The Chair opened the meeting and welcomed members.

2. Apologies

Malcolm Latham, Community Health Council, Lay representative
Ian Campbell, Hospital Consultant CAV, representative NMG
James Coulson, Clinical Pharmacologist, Cardiff and Vale
Richard Hain, Consultant in Paediatric Palliative care, representative Cardiff and Vale
Karen Samuels, AWTTC
Bethan Tranter, Chief Pharmacist, representative AWPAG/Velindre

3. Declaration of Interests/Confidentiality

The Chair reminded members that all OWMAG proceedings are confidential and should not be disclosed outside of the meeting. Members were reminded that declarations of interest and confidentiality statements are signed by each member on an annual basis. The Chair invited any declarations of interest; there were none.

4. Assessment one

Infliximab for the treatment of pulmonary sarcoidosis that has not responded to corticosteroids and other immunosuppressants.

The Chair welcomed clinical expert, Dr Nicola-Xan Hutchinson, Consultant in respiratory Medicine, Cardiff and Vale UHB. The Chair described the role of the clinical expert as an invited observer of the OWMAG meeting to answer questions and input into discussions to enable members to gain a better understanding of the clinical context. The Chair highlighted that clinical experts were nominated by their specialist group or network and should not express personal opinion or promote the use of a medicine.

The Chair invited any declarations of interest specific to this assessment; there were none.

Gail Woodland presented an overview of the key aspects of the infliximab evidence status report.

The Chair invited the clinical expert, Dr Nicola-Xan Hutchinson, to give an overview of the disease and medicine being considered. The clinical expert detailed the typical clinical pathway; patients with stage 3 sarcoidosis and

above would be considered for treatment, initially with corticosteroids as first line. If steroids fail then current options are to cycle between methotrexate, azathioprine and leflunomide. If disease progresses or patients experience treatment side effects then infliximab is considered. In South Wales infliximab is accessed via the individual patient funding request (IPFR) route.

The Chair asked about the life expectancy and quality of life for patients with this condition. Dr Hutchinson explained that if sarcoidosis is not managed it can progress to pulmonary fibrosis. The overall aim of treating sarcoidosis is to prevent progression rather than expect improvement or cure, this means that endpoints as expressed in clinical trials tend to be clinically inappropriate [with trials powered for assessing clinical improvement rather than disease stability or progression]. Lung transplant is another treatment option for which is estimated to give a life expectancy of five years.

The Chair asked if infliximab would enable a reduction in steroid doses. Dr Hutchinson stated that it was very difficult to reduce steroids in these patients who often develop dependency, including adrenal insufficiency, so it would be difficult to say categorically that infliximab would result in a reduction in steroid dose.

The Chair opened discussion on clinical effectiveness to the group.

The group questioned the relevance of the clinical trial endpoints of forced vital capacity (FVC) and use of the St Georges patient questionnaire. Dr Hutchinson explained that a small improvement in FVC would not necessarily make a difference to the patient's condition, maintaining disease stability is far more important. The St Georges questionnaire is not routinely used in clinical practice. The group asked how often the option to increase the dose from 3 mg/kg to 5 mg/kg was used. Dr Hutchinson informed the group that the Brompton Hospital protocol was followed which does include this as an option but was rarely required. The group highlighted the lack of recent research. The availability of biosimilars means that new research is less appealing to licence holders. The patient population for this condition size is small and recruitment of suitable numbers to trials is problematic.

Members asked if access to this treatment would reduce the need for lung transplants. The expert was unable to say based on the cases considered by the MDT group to date who were not suitable candidates for lung transplant due to other factors. The group asked about the use of other medicines, in particular leflunomide. The expert said that in practice leflunomide is rarely used due to the poor adverse effect profile, infliximab would be preferred.

The Chair opened discussion on cost effectiveness and budget impact.

The group noted the lack of cost effectiveness evidence. Adverse events associated with use of infliximab were queried, the expert informed the group that infliximab has been use widely and tolerated well in other specialities. Specialist respiratory nurses have drawn up a protocol for patient safety checks before treatment with infliximab is started. The health economist suggested that

the budget impact did not appear high but whether it was considered reasonable depends upon how convinced the group are of clinical effectiveness. The Chair pointed out that the clinical study endpoints do not reflect disease stability. The outcomes of the systematic review were noted. Dr Hutchinson informed the group that the South Wales respiratory group are collecting data and will be able to provide outcomes for these patients. Gail Woodland queried the duration of treatment with infliximab, would it be two or three years? The expert explained that whilst there is no clear guidance all patients would be stopped at two years to assess response. The Chair asked about the waiting time for transplants, Dr Hutchinson was unsure as to current figures as data has been skewed by the pandemic, however the wait could be between two and five years and there is a high mortality rate for patients on the waiting list.

The Chair opened discussion on the patient and public perspective and wider societal issues. Dr Hutchinson described the frustration and sense of inequity expressed by patient networks. The uncertainty and stress of having to go through the IPFR process.

The clinical expert was thanked and left the meeting and members were invited to vote. The OWMAG recommendation for health board Chief Executives was agreed:

Date of advice: Monday 19 December

Using the agreed starting and stopping criteria, infliximab can be made available within NHS Wales for the treatment of refractory pulmonary sarcoidosis. Infliximab should be prescribed on the basis of lowest acquisition cost.

5. Assessment 2

Vedolizumab (Entyvio®) for the treatment of inflammatory bowel disease in children and young people: for ulcerative colitis following loss of response or non-response to anti-TNF treatment; for Crohn's disease following loss of response or non-response to anti-TNF treatment and ustekinumab

The Chair welcomed clinical experts, Dr Amar Wahid, Consultant in Paediatric Gastroenterology and Jessica Girvan, Clinical Pharmacist for Paediatric Gastroenterology, both at Cardiff and Vale UHB. The experts introduced themselves to the group.

The Chair welcomed the patient organisation representatives, Amy Deptford, Policy Manager and Chloe Hutchinson, Policy Lead (Wales), both representing Crohn's and Colitis UK. The representatives introduced themselves to the group.

The Chair invited any declarations of interest specific to this assessment; there were none.

Clare Elliott presented an overview of the clinical background information pertinent to this and the following assessment before presenting key aspects of the vedolizumab evidence status report.

The Chair described the role of the clinical expert as an invited observer of the OWMAG meeting to answer questions and input into discussions to enable members to gain a better understanding of the clinical context. The Chair highlighted that clinical experts were nominated by their specialist group or network and should not express personal opinion or promote the use of a medicine. The Chair asked if the clinical experts had any declarations of interest. Dr Wahid confirmed that he had none and also clarified that his department are not involved in the VedoKids clinical trial but are in the process of setting up another study.

The Chair invited the clinical experts to provide an overview of the disease and medicine being considered. Dr Wahid explained that inflammatory bowel disease (IBD) has been found to be a progressive condition rather than relapsing/remitting. For Crohn's disease in particular, if diagnosed at a young age it tends to be particularly aggressive with the majority of young patients requiring treatment with biologics at an early stage. IBD is a debilitating condition with a low public profile compared with other disease areas. Diagnosis of children has tripled since 2017, with more patients requiring biological treatments. There is a need for treatment options for when anti-TNFs have failed. Vedolizumab is considered safer due to the gut specificity and with no link to cancers which was a concern for the more classic IBD treatments. Progressive multifocal leukoencephalopathy (PML) has not been associated with vedolizumab due to the gut specificity. Dr Wahid has experience of using vedolizumab already and reports good success with treatment.

The Chair questioned the increase in diagnosis in young people. Dr Wahid explained that in Wales diagnosis had been behind the national average. A proactive approach, use of calprotectin monitoring and endoscopy has brought diagnosis in line with other areas of the UK. There has also been a general rise in the number of cases diagnosed across the UK. There is a concomitant rise in the adult population with patients transitioning to adult care without a diagnosis or effective treatment in place.

The Chair invited Jessica Girvan to comment. She had identified this need for paediatric patients after sending multiple IPFRs to Welsh Health Specialised Services Committee (WHSSC). Patients failing on currently available treatment need additional options to delay or prevent the need for surgery at a later date. The patient numbers provided had not accounted for transition to adult services. Dose escalation has been required for some patients.

The Chair invited the patient organisation representatives to comment. The Chair described the role of the patient organisation representative as providing the patient perspective and highlighting social issues for both assessments.

Amy Deptford agreed with the presentation and clinical expert perspectives. In responses to surveys run by Crohn's and Colitis UK in 16 to 18-year olds a quarter felt that the condition had prevented them from meeting their full potential, 80% reported that the mental and physical impact of their disease had affected education. Over half of respondents had restricted their employment options due to their condition. Parents and carers of young people are

concerned over the effect of the condition and prospects for disease progression in their later life. Treatment options are still far from optimal, a third of IBD patients will not be able tolerate thiopurines, a further 10% would be unresponsive. For immunosuppressants it can take up to 6 months for therapy to have an effect, 40% may not respond and approximately 10 to 15% will lose response over time. Children need to be able to access the widest treatment options for this condition to restore quality of life and have as normal a life as possible. Chloe Hutchinson highlighted that these treatments can delay or avoid the need for surgery. Surgery with subsequent stoma at this stage in life in particular is traumatic for children and can severely affect their mental health.

The Chair opened up discussion on the clinical effectiveness. The group asked about patients transferring to adult care and treatment options before vedolizumab would be considered. The clinical expert confirmed that adult patients are eligible to receive vedolizumab as per NICE guidelines. This was confirmed by AWTTC. Patients are treated with either infliximab or adalimumab before vedolizumab is considered. The group also asked if avoidance of surgery be included in budget impact calculations, AWTTC stated that it wasn't. The group asked about patient numbers for North Wales, AWTTC stated that numbers are extrapolated from South Wales figures.

The group requested clarification as to which age groups the evidence is to be applied to, as the biologics (infliximab and adalimumab) are licensed for use at 6 and older. Dr Wahid stated that they have successfully used vedolizumab for early onset IBD in children younger than 6 years who have failed on anti TNF. Jessica Girvan explained that the children eligible for treatment would likely be two cohorts, those very young children with early onset aggressive disease and older post pubertal children whose disease has progressed. She expects IPFR to remain the route of access for children under 6 years.

The group asked for comment on the long-term effects of vedolizumab. Dr Wahid explained that in his experience effects have lasted for about a year and in some cases the dose has then had to be escalated but there is little data on longer term. If vedolizumab treatment fails patients may be switched to ustekinumab. There are also new medicines in the pipeline due to become available in the next few years.

The Chair opened discussion on cost effectiveness. The group asked if there had been a reduction in surgical intervention in children since these medicines have become available. Dr Wahid stated that in the experience of Cardiff and Vale they have definitely seen a reduction in the need for surgical intervention in children, although it is too early to say what the impact is on surgery in later life. He also pointed out that for ulcerative colitis, colectomy is not necessary a cure for the disease and complications following surgery are common as are the effects on mental health. Amy Deptford informed the group that there had been some research on the costs associated with IBD where it was estimated that

treating a flare in disease cost ten times as much as managing stable disease. The group noted the cost effectiveness evidence presented for adults and the inherent limitations of this evidence.

The chair opened discussion on budget impact, there were no additional comments or questions raised.

The chair opened discussion on wider societal and health and social care issues, there were no additional comments or questions raised.

6. Assessment 3
Ustekinumab (Stelara®▼) for the treatment of inflammatory bowel disease in children and young people: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies.

The Chair invited any declarations of interest specific to this assessment; there were none.

Clare Elliott presented key aspects of the ustekinumab evidence status report.

The Chair invited the clinical experts to give an overview of the medicine being considered. Dr Wahid stated that ustekinumab is considered safe, and is a particularly good treatment for patients who have multi-system inflammation. In other patients with severe refractory disease treatment with ustekinumab has been successful. Another advantage is that after the initial infusion, subsequent doses are administered by subcutaneous injection which can be given at home. Jessica Girvan explained that paediatric patients may require dose escalation to more frequent dosing. This product can be supplied via homecare services.

The Chair invited the patient organisation representatives to comment. Amy Deptford stated that the same issues were pertinent to this assessment as had been described for the previous assessment. An additional consideration for the ustekinumab would be the advantage of fewer hospital visits with home administration and consequently less disruption to children's lives and education. Dr Wahid added that, in particular for Crohn's disease, surgery is not curative and often multiple surgical interventions are required with a risk of complications following surgery.

The Chair opened up discussion on clinical effectiveness. The group asked about the lack of evidence in the pre-pubertal age group in particular with relation to safety and efficacy. Dr Wahid agreed that there is little published evidence for IBD but good data is available for other conditions such as plaque psoriasis (licensed for 6 years and over). The group also asked about compliance with young children self-administering subcutaneous injections. Dr Wahid was confident that these patients are very compliant and they have an effective team of nurses to train patients and carers to administer the injections at home. Jessica Girvan added that as ustekinumab is given every eight to ten weeks compared to up to weekly for anti-TNF treatments where compliance is

very good. Amy Deptford highlighted that patients who would be treated with ustekinumab have already received multiple other treatments and so are used to medical intervention. She also reminded the group that the condition being treated is life-changing and self-injection wouldn't be an issue as long as they are taught how to use the injection.

The group asked about patients who stop gaining benefit with 8 weekly administration; would dosing be escalated to 4 weekly? Dr Wahid stated that in a significant number of patients dose escalation to six or four weekly is required.

The group asked about the lack of evidence for use in children under six years old, are children put on a treatment register for follow up? Dr Wahid informed the group that they have a patient database to monitor treatments. He also stated that very few younger patients would be treated with ustekinumab for early onset IBD.

The Chair opened discussion on cost effectiveness. There were no additional comments raised.

The Chair opened discussion on budget impact. Dr Wahid highlighted the potential for prevention or delay in surgery, not only colectomy but also the need for small intestine removal and associated complications such as the need for parenteral nutrition. Both incur massive costs to the NHS and also a huge burden on the patient.

The Chair opened discussion on wider societal and social and health care issues. Dr Wahid mentioned the potential environmental savings with home administration requiring fewer journeys to hospital and the associated reduction in emissions, travel time and fuel costs.

The Chair thanked the clinical experts and patient representatives who left the meeting.

The group agreed that the indications for both vedolizumab and ustekinumab should be revised to stipulate 6 years and older.

Members were invited to vote on the vedolizumab. The OWMAG recommendation for health board Chief Executives was agreed:

Date of advice: Monday 19 December

Using the starting and stopping criteria, vedolizumab (Entyvio®) can be made available within NHS Wales for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response or non-response to anti-TNF treatment; for Crohn's disease following loss of response or non-response to anti-TNF treatment and ustekinumab. The risks and benefits of the off-label use of vedolizumab (Entyvio®) for this indication should be clearly stated and discussed with the patient to allow informed consent.

Members were invited to vote on the ustekinumab. The OWMAG recommendation for health board Chief Executives was agreed:

Date of advice: Monday 19 December

Using the starting and stopping criteria, ustekinumab (Stelara®▼) can be made available within NHS Wales for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies. The risks and benefits of the off-label use of ustekinumab (Stelara®▼) for this indication should be clearly stated and discussed with the patient to allow informed consent.

The group discussed whether dose escalation could be included in the starting and stopping criteria for these medicines. This would differ from the licensed dose used in adults. The group voted to allow dose escalation in the starting/stopping criteria as per the clinical expert's comments in discussions.

7. Review

Rituximab for the fourth line or later treatment of myasthenia gravis in adults

The Chair invited any declarations of interest specific to this assessment; there were none.

Rosie Spears provided a summary of the review report including new evidence for the current line of therapy and a summary of additional evidence for first line and lower dose treatment.

The Chair opened discussion on the review. The group asked about IPFRs for first line treatment. AWTTC stated that there were none that they are aware of but it is difficult to discern line of treatment from limited database information. The group asked about the position of the newly licensed therapies. AWTTC explained that these medicines have not yet undergone Health Technology Assessment and according to clinical experts are likely to be reserved for refractory myasthenia gravis, however, would be taken into consideration if a full re-assessment was undertaken. The group clarified the lower dose, at a quarter of the normal recommended dose this would be attractive in terms of safety and cost effectiveness.

Members were invited to vote on the rituximab review. The OWMAG recommendation was to re-assess rituximab for the treatment of myasthenia gravis to consider use as first line treatment and at a lower dose. The current advice for fourth line and above treatment will remain in place until the re-assessment is completed.

8. AOB

Gail Woodland informed members that there will not be an OWMAG meeting in January.